# Diabetic retinopathy: variations in patient therapeutic outcomes and pharmacogenomics.

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REVIEW

# Diabetic retinopathy: variations in patient therapeutic outcomes and pharmacogenomics

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**Abstract:** Diabetes and its microvascular complications in patients poses a significant challenge and constitutes a major health problem. When it comes to manifestations in the eye, each case of diabetic retinopathy (DR) is unique, in terms of the phenotype, genotype, and, more importantly, the therapeutic response. It is therefore important to identify factors that distinguish one patient from another. Personalized therapy in DR is a new trend aimed at achieving maximum therapeutic response in patients by identifying genotypic and phenotypic factors that may result in less than optimal response to conventional therapy, and consequently, lead to poorer outcome. With advances in the identification of these genetic markers, such as gene polymorphisms and human leucocyte antigen associations, as well as development of drugs that can target their effects, the future of personalized medicine in DR is promising. In this comprehensive review, data from various studies have been analyzed to present what has been achieved in the field of pharmacogenomics thus far. An insight into future research is also provided.

**Keywords:** personalized medicine, therapeutic variation, genomic markers, genotype, phenotype, VEGF mutation, polymorphism, linkage, mutation, responder

## Introduction

Diabetes is a major health problem that is frequently associated with long-term microvascular complications. The number of people suffering from diabetes (approximately 366 million in 2011 worldwide) is expected to reach approximately 552 million by the year 2030. Diabetic retinopathy (DR) and its complications are responsible for legal blindness in as many as 2.6% of the population worldwide, in patients diagnosed with both type I and II diabetes.[1,2]

There is large variation in the incidence and severity of visual loss and other complications associated with DR. For example, the incidence of vitreous hemorrhage in patients with DR ranges from 17% to 63%.[3] Similarly, the prevalence of diabetic macular edema (DME) ranges from 0.85% to 12.3% among patients with diabetes.[4] The current standard of care, ie, anti-vascular endothelial growth factor (anti-VEGF) therapy, has shown a significant improvement ($\geq$3 lines visual acuity) in only 44.8% with 0.3 mg ranibizumab in the RISE study,[5] while 55.2% patients receiving the same therapy failed to show a similar response. Multiple factors contributing to this variability in response have been studied. It has been proposed that, in addition to environmental factors, genetic makeup of patients may play a role in such variability.

In this review, we explore the developments in the field of pharmacogenomics concerning DR. The analysis may enable clinician-scientists to understand the possible

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mechanisms behind individual variations in response to standard therapeutic interventions in patients with DR.

## Methods

A systematic review of the literature was performed using the United States National Library of Medicine (PubMed), Ovid search engine, and the Medline database to retrieve the literature on the phenotypes and genotypes in DR, genetic basis of patient-to-patient variation in response, and pharmacogenomics. The keywords and MESH headings used were as follows: *diabetic retinopathy, genotype, phenotype, polymorphism, linkage, mutation*, and *responder*. Additional articles were also obtained by studying the reference list of these articles. Only articles published in English were included for the review.

In the literature review, both prospective and retrospective studies were included. Studies focusing on patients developing DR as a microvascular complication in both type 1 and type 2 diabetes were included. Studies including various ethnic groups were included in order to ensure comprehensive data analysis. Data from larger clinical trials were also obtained.

## Results
### Established therapy for diabetic retinopathy

Systemic control of the underlying risk factors, ie, hyperglycemia, hypertension, and hyperlipidemia, has been shown to reduce the risk of progression of DR.[6] Local therapies, which include laser photocoagulation, intravitreal or periocular steroids, and anti-VEGF, on the other hand, are mainly used for the management of DME.[7] Currently, the use of anti-VEGF agents is gaining popularity and becoming the standard of care for management of DME owing to its favorable outcome.[8] Thus, the mainstay of therapy for DR that is manifested by DME, among other complications, is periodic intravitreal injections of anti-VEGF.[9] Such therapy is aimed at antagonizing VEGF and its downstream effects.

Among the various pharmacologic agents used, bevacizumab is a humanized murine monoclonal antibody that binds to all isoforms of VEGF-A. Ranibizumab is a smaller molecule with high binding affinity to VEGF-A[10] and is approved for treatment of DME by the United States Food and Drug Administration (FDA). Pegaptanib sodium is an aptamer specifically inhibiting the VEGF-A 165 isoform, and aflibercept is a human fusion protein incorporating ligand-binding elements from VEGF receptors and the Fc region of

an IgG1 molecule. Aflibercept has been recently approved for the treatment of DME by the FDA. Aflibercept offers similar efficacy as the other anti-VEGF agents with the potential advantage of less frequent dosing.[11]

In addition to anti-VEGF therapy, intravitreal and periocular injections of corticosteroids and laser photocoagulation have been used to treat DR as well.

## Concerns with established therapy for diabetic retinopathy

Clinical trials have demonstrated marked variations in response to anti-VEGF therapy in DME. For instance, with 0.3 mg ranibizumab, 44.8% of patients gained >3 lines on the EDTRS chart at 24 months, with the rest of the study subjects showing less than optimal response in the RISE study, whereas 34% patients receiving 0.3 mg ranibizumab demonstrated an improvement of >3 lines on ETDRS chart in the RIDE study.[5] In both trials, there were few patients that showed loss of >15 letters, ie, six out of 250 patients in RISE and seven out of 252 patients in RIDE study. Similarly, trials have also documented the efficacy of bevacizumab in patients with DME. The bevacizumab or laser therapy (BOLT) study demonstrated that, in patients receiving intravitreal injections of bevacizumab, there was >3 EDTRS lines improvement in visual acuity in 39% of patients.[12] In the DA VINCI study, 34% of the patients showed a significant level of visual acuity improvement following therapy with aflibercept.[13] Variation of treatment response with anti-VEGF therapy has also been demonstrated in other retinal diseases such as age-related macular degeneration. In the Comparison of Age-Related Macular Degeneration Treatments Trials (CATT), 34.2% and 31.3% patients showed an improvement of >15 letters following treatment with monthly ranibizumab and bevacizumab, respectively.[14]

The results of these major clinical trials indicate that, among patients with DR and DME, there are asymmetric responses. There is large variation in the clinical response, and many patients do not demonstrate satisfactory levels of visual acuity improvement (Table 1).

## Phenotype variation in diabetic retinopathy

Available data suggest that phenotypic variation occurs in patients with DR. Multimodal imaging has demonstrated that some patients may present with certain features on biomicroscopy and indirect ophthalmoscopy, such as rates of microaneurysm accumulation and foveal avascular zone alterations that may be associated with worse

**Table I** Visual outcome analysis in patients with diabetic retinopathy enrolled in various clinical trials.

| Clinical trial | Pharmacologic agent with dose | Gain of ≥3 lines (%) | Loss of ≥3 lines (%) | No significant change (gain or loss of <3 lines) (%) | Study duration (months) |
|---|---|---|---|---|---|
| **Trials with intravitreal anti-vascular endothelial growth factor (anti-VEGF) therapy** | | | | | |
| RISE[5] | Ranibizumab | | | | 24 |
| | 0.3 mg | 44.8 | 2.4 | 52.8 | |
| | 0.5 mg | 39.2 | 2.4 | 58.4 | |
| RIDE[5] | Ranibizumab | | | | 24 |
| | 0.3 mg | 33.6 | 1.6 | 64 | |
| | 0.5 mg | 45.7 | 4 | 50.3 | |
| VIVID[15] | Aflibercept | | | | 12 |
| | 2 mg 4-weekly | 32.4 | 0.7 | 66.9 | |
| | 2 mg 8-weekly | 33.3 | 0 | 66.7 | |
| VISTA[15] | Aflibercept | | | | 12 |
| | 2 mg 4-weekly | 41.6 | 0.6 | 57.8 | |
| | 2 mg 8-weekly | 31.1 | 0.7 | 68.2 | |
| BOLT[12] | Bevacizumab | | | | 24 |
| | 1.25 mg | 32 | 0 | 68 | |
| DA VINCI[13] | Aflibercept | | | | 12 |
| | 2 mg | 34 | 0 | 66 | |
| READ 2[16] | Ranibizumab | | | | 24 |
| | 0.5 mg | 24 | 3 | 73 | |
| RESOLVE[17] | Ranibizumab (pooled analysis of 0.3 and 0.5 mg) | 33 | 3 | 64 | 12 |
| RESTORE[18] | Ranibizumab | | | | 12 |
| | 0.5 mg | 22.6 | 0.9 | 76.5 | |
| **Trials with intravitreal steroid therapy** | | | | | |
| FAME[19] | Fluocinolone | | | | 24 |
| | 0.2 µg/day | 28.7 | 0 | 71.3 | |
| | 0.5 µg/day | 28.6 | 0 | 71.4 | |
| MEAD[20] | Dexamethasone | | | | 36 |
| | 0.7 mg | 22.2 | 0 | 77.8 | |
| | 0.35 mg | 18.4 | 0 | 81.6 | |

visual prognosis.[21] In this 3-year follow-up study performed on 14 eyes with type 2 diabetes, the level of DR was graded by the Wisconsin Card-Sorting Test. Areas of abnormally increased hyperfluorescence were analyzed at baseline and follow-up visits after stabilization of mean $HbA_{1c}$ levels. Based on the intensity and persistence of the leakage sites, a genetic basis for this phenotypic variation in DR was suggested by the authors.

Studies with larger cohorts were subsequently performed to validate the results of the previous study.[22,23] A prospective study[22] including 410 patients with type 2 diabetes was conducted to follow up the patients for 2 years or until the time they developed macular edema. The results of this study demonstrated the presence of three distinct phenotypes of DR. Phenotype A was identified with lowest microaneurysm turnover and central subfoveal thickness. Phenotype B was identified with higher central subfield retinal thickness, whereas phenotype C had higher microaneurysms turnover but variable macular thickness. A study involving patients with type 1 diabetes suggested that the genetic makeup may

affect the breakdown of the blood–retinal barrier or pericyte apoptosis, resulting in different phenotypes of DR.[24]

As an example, Figure 1 shows the differences in progression of DR in two patients. In the first patient (panels A and B), there is an increased turnover of microaneurysms over time, whereas the second patient (panels C and D) has an increased leakage on fluorescein angiography and thickness over a period of 3 months without much microaneurysm turnover.

The FIND-Eye study[25] in 2008 suggested increased severity of DR in individuals predisposed genetically to more microvascular complications, including diabetic nephropathy. A number of ethnic groups were included in this study, such as American Indians, European Americans, African Americans, and Mexican Americans. Heritability of the severity of retinopathy was assessed by sibling analysis. Another study that retrospectively reviewed charts of both Black and Latino diabetic patients demonstrated that Latinos may be at a greater risk for a specific retinopathy phenotype characterized by extravasation of intraretinal hemorrhages and poorer prognosis.[26]
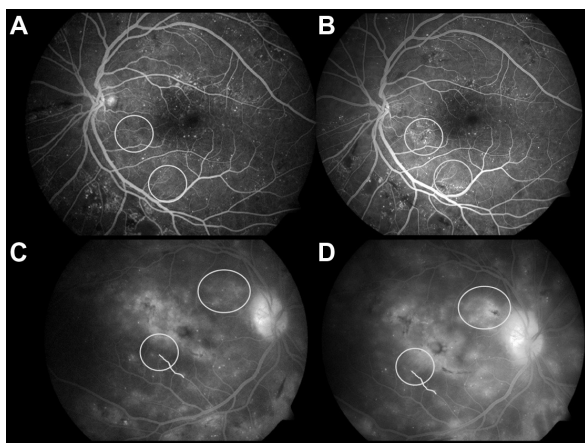
**Figure 1** Characteristic differences in the phenotype of diabetic retinopathy (DR) in two patients.
**Notes:** Panels **A** and **B** show fluorescein angiography of one patient with type 2 diabetes mellitus who presented with a nonproliferative DR (panel A). The area marked with yellow circle shows the absence of microaneurysms at that location during the initial presentation. After 3 months, the same area, marked with a yellow circle, shows development of new microaneurysms (panel B), without much increase in leakage on fluorescein angiography. Panels **C** and **D** show fluorescein angiography of another patient with type 2 diabetes mellitus (taken at the same time interval). Panel C shows the angiography at presentation; areas are marked with yellow circles to demonstrate an increase in the area of leakage (the vessels are traced with yellow lines to allow comparison) and thickness over a period of 3 months (panel D) without significant increase in the microaneurysm turnover.

Conclusive data that identify specific complication risks for each ethnic group are not available.

Morphometric analysis of eyes of patients with DR have shown that certain features on spectral domain optical coherence tomography imaging, such as disruption of photoreceptor inner segment–outer segment junction, can significantly decrease retinal sensitivity. Further studies are required to correlate genetic basis of this phenotype observation.[27]

There is increasing evidence for the genetic basis for phenotypic variations in patients with DR.[28] Differences in phenotypes may result in increased risk of progression of the disease and visual loss due to higher levels of ischemia and VEGF release.[16,29] With advancement in clinical examination techniques and imaging modalities, it may be possible to identify more phenotypic variations in DR. Early identification of such a cohort of patients may enable clinicians to prepare for more aggressive therapy in order to salvage vision.

## Genotype variation in diabetic retinopathy

Data from a number of studies suggest the presence of various genetic polymorphisms in susceptibility to DR. There are a number of studies that provide evidence to the presence of various pathogenetic factors, including activity of aldose reductase (AR) and protein kinase C as well as processes such as glycation, platelet adhesion, and aggregation.

## Genetic basis of morphological variation in diabetic retinopathy

Results from twin studies[30] and various clinical trials such as the Diabetic Control and Complications Trial (DCCT) suggest genetic polymorphisms that may play an important role in manifestations of DR, such as familial clustering of proliferative DR.[31] It has been shown that only about half the number of patients diagnosed with nonproliferative DR progress to the proliferative disease.[30,31] Further investigations into the genetic factors that influence the manifestations of retinopathy have revealed human leucocyte antigen (HLA) associations and single nucleotide polymorphisms (SNPs), which may contribute to the initiation or promotion of inflammatory cascade.[32]

## Genome-wide association studies

One of the strategies to identify genetic predisposition to severe DR is genome-wide association studies (GWAS). Using this data, millions of common polymorphisms can be identified in the human genome. Following the successful GWAS for age-related macular degeneration, similar studies have been performed for various populations for DR.

Two large cohorts including patients with type 1 diabetes, the Epidemiology of Diabetes Intervention and Control Trial and the Genetics of Kidney in Diabetes studies, did not find any genome-wide association except a relationship between severe DR and the SNP rs476141.[32] This SNP is located between the *AKT3* and *ZNF238* genes that may play a role in cell survival, insulin signaling, and angiogenesis. The Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR) found a new potential SNP *rs4865047* located in the *CEP125* gene associated with severe DR.[33]

In the Taiwanese population, five loci have been identified in patients who are susceptible for the development of DR. These loci include *PLXDC2* and *ARHGAP22*, which play a role in capillary endothelial proliferation and permeability.[34] In a study with Mexican-American population, 32 SNPs were identified from 11 regions in patients with DR with modest association. These SNPs belonged to loci from genes that are usually not associated with DR.[35]

A large collaborative study with European-American population, the Candidate-gene Association Resource (CARe), comprised more than 2,500 subjects with type 2 diabetes. In this study, polymorphisms associated with DR identified included certain SNPs in the P-selectin (*SELP*) gene. These polymorphisms were associated with increased severity of DR. However, the results of this study were not replicable in studies involving other ethnic and racial groups.[33]

Thus, polymorphisms involving the selectin genes have not conclusively been shown to be associated with severe DR.

More studies that can validate data and include larger cohorts have been possible because of rapid advances in technology and means to identify genetic variations. However, presently, GWAS have various limitations. These include replicability of data due to ethnic variations in polymorphisms. The commercial arrays can identify only rare, low-frequency variants. Larger studies with different ethnic groups may be required to provide stronger statistical support for confirming association.[32]

## Linkage studies and HLA association

Linkage analysis helps in the identification of alleles that may predispose to the development of more aggressive form of DR. Linkage analysis was carried out in Pima Indians to identify susceptibility genes for DR.[36] In this study, a region close to angiotensin II receptor gene *AGTR1* located on chromosome 3 was identified to be associated with retinopathy. Familial aggregation of severe DR was linked to chromosome 1 in another study.[37] However, further studies are required to conclusively establish any association.

Several studies have also attempted to identify associations between HLA and severity of DR. Literature supports the association between HLA DR4 and DR3 phenotypes to be associated with proliferative DR. The odds of developing proliferative retinopathy among individuals with HLA-DR 3/0 are 3.74 times the control arm, with the true population effect being 1.8–7.8 times.[38,39]

## Candidate gene studies

Candidate genes encoding proteins that may play an important role in the pathogenesis of DR have been studied extensively in order to identify their polymorphisms as potential pharmacogenetic markers. An attempt to identify these markers in DR in individuals with diabetes has been made and involved various population subgroups. Certain polymorphisms belong to pathways that are distinct from VEGF.

Apart from VEGF, certain candidate genes such as aldose reductase (*AR*),[40] endothelial nitric oxide synthase (*eNOS*),[41] receptor for advanced glycation end products (*RAGE*),[42] and erythropoietin (*EPO*)[43] genes have been studied extensively in various ethnic groups. Polymorphisms in these candidate genes can potentially affect various metabolic pathways, thereby increasing the risk of severe DR. For example, mutations in the methylenetetrahydrofolate reductase (*MTHFR*) gene are associated with high plasma homocysteine levels,[44,45] increasing the risk of proliferative DR.[46–48] There is, however,

no clear consensus on the exact role of various candidate gene polymorphisms, and further research in this direction is warranted.

Table 2 lists the important potential pharmacogenetic markers of severe DR based on evidences from various

**Table 2** Possible pharmacogenetic markers for diabetic retinopathy

| Gene | Variation | Clinical outcome |
|---|---|---|
| ACE | 2350 G/A | Associated with development of diabetic retinopathy in Chinese population[49] |
| AGTR1 | A1166C | Increased risk of diabetic retinopathy and nephropathy[50] |
| AR | −106CC | Increased risk of proliferative retinopathy in Caucasian–Brazilians[51] |
| CFH | rs800292 rs1048709 | Important role in pathogenesis and development of diabetic retinopathy[52] |
| CHN2 | rs1002630 | Increased risk of nonproliferative diabetic retinopathy in Taiwanese individuals[53] |
| EL | c.584C>T | Increased risk factor for developing severe, sight-threatening proliferative disease[54] |
| eNOS | 4b/b | Confers an increased risk of severe diabetic retinopathy[55] |
| EPO | rs1617640 rs507392 rs551238 | Increased risk of development of proliferative diabetic retinopathy in American and Australian population[56] |
| ITGA2 | BgI II | Increased risk of diabetic retinopathy[57] |
| ITGB3 | PIA1/A2 | |
| MCP-1 | c.2518G/G | Increased susceptibility to proliferative diabetic retinopathy in type 2 diabetes patients[58] |
| MTHFR | C667T | Development of microangiopathic changes in patients with Type 2 diabetes[59] |
| OPG | rs2073618 rs3134069 | Increased risk of development of diabetic retinopathy[60] |
| RAGE | 1704G/T 2245G/A | Increased pro-inflammatory response in patients with diabetic retinopathy[61,62] |
| SELP | rs12708942 rs9806929 rs4783824 | Development of diabetic retinopathy in patients with type 2 diabetes[63] |
| TCF7L2 | rs7903146 | This polymorphism plays an important role in development of diabetes mellitus. But contribution in development of retinopathy may be small[64] |
| UCP1 | −3826A/G | Increased risk of proliferative diabetic retinopathy with both the genes[65,66] |
| UCP2 | A Val Ins | |
| VEGF | −2578 C/A 1498 C/T (−460 C/T) −634G/C (405 G/C) +936C/T | Enhanced VEGF expression Increased susceptibility of retinopathy in various population studies[67a] |

**Note:** [a]Meta-analysis.
**Abbreviations:** ACE, angiotensin converting enzyme; AGTR, angiotensin II receptor; AR, aldose reductase; CFH, complement factor H; CHN2 = NOR, neuron-derived orphan receptor; EL, endothelial lipase; eNOS, endothelial nitric oxide synthase; EPO, erythropoietin; ITGA/B, integrin A/B; MCP1, monocyte chemotactic protein 1, MTHFR, methylenetetrahydrofolate reductase; OPG, osteoprotegrin; RAGE, receptor for advanced glycation end products; SELP, selectin P; TCF7L2, transcription factor 7 like 2; UCP, uncoupling protein; VEGF, vascular endothelial growth factor.

population case–control trials. Data from meta-analysis have also been included, where available. With more research, our knowledge of genetic markers is going to expand.

## VEGF pathway and VEGF gene polymorphisms

VEGF expression plays a central role in the pathogenesis of DR. The upregulation of VEGF in the eyes of patients with diabetes is associated with breakdown of the blood–retinal barrier and increased vascular permeability.[68] This leads to clinical manifestations of retinopathy. Higher levels of VEGF in the vitreous are correlated with increased severity of macular edema and DR.[69,70]

SNPs in the VEGF gene and its polymorphisms are of particular interest because therapy of DR largely focuses on anti-VEGF drugs.

The VEGF gene is located on chromosome 6p21.3 and is highly polymorphic as demonstrated in previous studies.[71–73] Of particular interest is the VEGF gene *C-634G* polymorphism *rs2010963* in the 5-untranslated region. Studies including Japanese and Slovenian populations suggest strong association of this polymorphism with development of macular edema.[70,74,75] Recent study in an Egyptian cohort of 392 patients demonstrated that the *CC* genotype of *C-634G* polymorphism resulted in a significant risk for developing macular edema independently of the grade of DR.[76] The *−634G to C* substitution enhances VEGF expression.[77]

Many SNPs in the VEGF gene have been identified to be associated with the development of DR. Studies that have tested the role of VEGF gene polymorphisms in patients with DR conclude that patients with the *CC* genotype have a higher level of VEGF in serum comparing the *CG* and the *GG* genotypes. The *CC* genotype is associated with more favorable response to anti-VEGF therapy, 76% compared to the *CG* (23%) and *GG* genotype (0.0%). The *GG* phenotype has been found to be an independent predictor of neovascularization and development of proliferative DR.[78]

A recent study found an increased association of DR with the *CA* genotype of the *−2578* polymorphism.[79] This polymorphism is also located in the promoter region. A meta-analysis including a number of case–control studies suggested an association between the *−2578C/A* polymorphism and DR in various ethnic groups except the Caucasian population.[80] Another meta-analysis studying the association of the VEGF gene polymorphisms with DR found that retinopathy is associated with the VEGF gene *−460T/C* polymorphism but not the *−2578C/A* polymorphism.[81] SNPs in the splicing region have also shown to be associated with DR. These include the *SRp55 2994* polymorphism that controls alternative splicing of VEGF pre-RNA exon. Such properties may affect the balance between pro- and antiangiogenic VEGF isoforms.[82]

The VEGF-A gene structure and its associated major polymorphisms associated with DR are summarized in Figure 2. There is, indeed, a need for additional studies in confirming the role of these polymorphisms in patients with DR and DME. The aim of the studies, which should evaluate genetic polymorphisms and mutations involving a variety of loci on the human genome, is to be able to comprehensively identify all the potential pharmacogenomics markers for poor prognosis in DR. While pharmacogenomic markers have been identified to a great extent in ocular diseases such as age-related macular degeneration and glaucoma, information on DR is not very definitive. Table 1 summarizes a list of potential pharmacogenomic markers that have been identified, but we still need further evidences before they can be clinically applicable.

## Genetic basis of response to treatment

With the knowledge that there are a number of genetic polymorphisms associated with the development of DR, it may be plausible that these polymorphisms could be responsible, at least partly, for variable response to anti-VEGF agents. Higher levels of VEGF associated with certain genetic compositions and polymorphisms in the VEGF gene itself
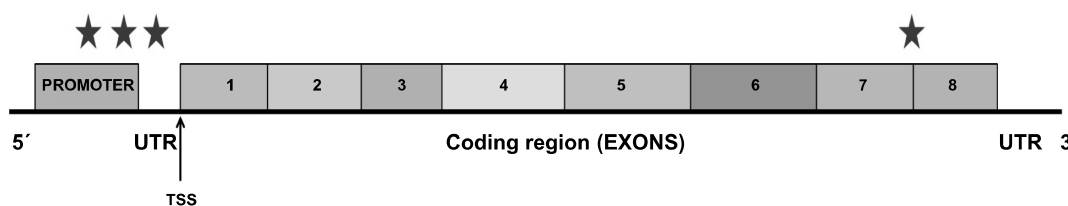


**Figure 2** Structure and functional anatomy of the vascular endothelial growth factor-A (VEGF-A) gene.
**Notes:** The primary structure consists of the upstream promoter region followed by the 5′ untranslated region (UTR). There are eight exons in the coding region of the VEGF-A gene with the transcription start sequence (TSS) near the Exon 1. The red stars represent the most common locations of the genetic polymorphisms of VEGF gene associated with DR. From left to right, the stars represent the locations of −2578 C/A polymorphism, followed by 1498 C/T (−460 C/T) polymorphism located in the promoter region; to their right is the location of the most important polymorphism, ie, −634G/C (405 G/C), in the 5′ UTR region. The red star on the right side indicates certain splice site mutations that may be responsible for tilting the balance toward proangiogenesis due to alternative splicing mechanism.

may indicate that, in order to achieve clinical benefit, either improvisation in the dosing regimen or combination therapy (of different targets) may be essential.

There is very little information available regarding the efficacy of various anti-VEGF agents used to treat DME based on the genetic profile of patients. On the other hand, there have been studies that evaluated such questions for AMD.[83–85] The large multicenter CATT study evaluated the response of anti-VEGF treatment in 835 patients based on VEGF gene polymorphisms.[86] The study could not conclusively identify any pharmacogenetic associations between gene SNPs and response to different anti-VEGF therapies. Current literature does not provide adequate information of pharmacogenetic associations in patients with DR.

On the other hand, it has been identified that there may be signaling pathways and abnormal gene expressions in patients with DR that are nonresponsive to therapy. In a study by Dabir et al,[87] a difference in the gene expression was found between responders and nonresponders to treatment. More than 60 genes were upregulated and approximately 50 downregulated in patients with DR who were nonresponsive to therapy. Identifying the specific signaling pathway involved in DR at different stages of retinopathy and in response to therapy may provide insights that can help to solve the puzzle between responders and nonresponders.

Responders to treatment showed dramatic decrease in the extracellular matrix receptor gene and notable decrease in the transforming growth factor beta (TGF-β), while no changes were observed in these genes in the nonresponder group. Nonresponders, on the other hand, demonstrated increased expression of cellular adhesion molecules, WNT signaling pathway (which is implicated in diabetic complications such as vascular leakage and retinal neovascularization), several transcription factors, as well as stress-related genes.

In addition to signaling pathways, patients with DR are known to have altered and mitigated genetic expression of antioxidant enzymes.[88] There are a variety of microRNAs (miRNAs) that are implicated in a variety of pathophysiological processes responsible for changes of DR. miRNAs control posttranscriptional gene expression and are important potential mediator and biomarker of diabetic complications and response to conventional therapy.[89,90]

Thus, the benefit in the response to antiangiogenic therapy may be limited due to redundancy of the VEGF target, thereby making the VEGF "resistant" to a particular therapeutic agent.[91] The summary of the pharmacogenomic basis for nonresponse or suboptimal response in certain cohorts of patients is elucidated in Figure 3.

## Personalized medicine in diabetic retinopathy

With advances in prospective, genetic, diagnostic, and therapeutic strategies for managing patients with DR, personalized treatment of patients with DR may soon be coming to the clinics. It may be possible to intervene early in patients identified to be at high genetic or phenotypic risk of progression, or in those who have a high risk of nonresponse to available therapies.[92]

Due to the enormous amount of financial constraints and health care cost concerns, research is now focusing on individualizing health care strategies based on extensive data available from studies.[93] Through recognition of genomic biomarkers to identify patients at risk who may be incomplete responders or may not respond at all, innovative and early treatment options may be tailored for better outcomes.[94] The ever-increasing burden of diabetes and its microvascular complications makes it very relevant to introduce the concept of personalized health care for this disease.
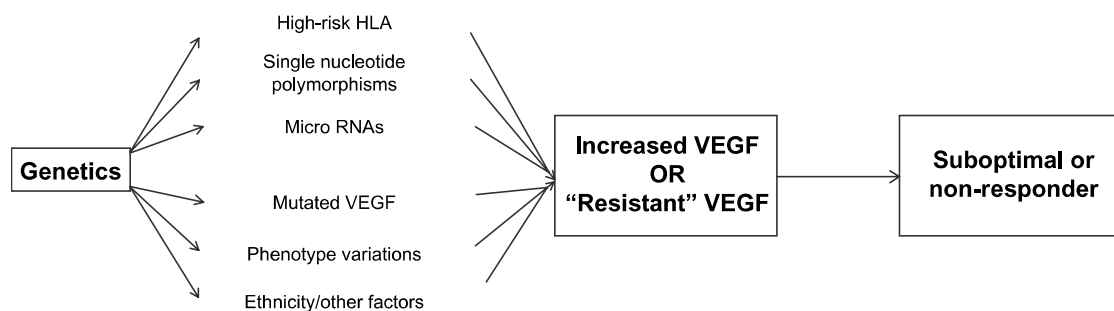


**Figure 3** Summary of the most important pathways that may be responsible for variability of response from patient to patient in diabetic retinopathy (DR).
**Notes:** Genetic factors are proposed to play a central role in the pharmacological variation in response. Evidences from linkage analysis and human leucocyte antigen (HLA) studies, genome-wide association analysis, and population studies have strengthened this theory. In addition, mutations in VEGF gene and phenotype variations in DR may directly or indirectly increase the VEGF expression and its downstream effects on the retina. This ultimately results in poor response or no response at all in certain groups of patients to conventional anti-VEGF therapy. Because of the large number of factors that may lead to this undesirable state, there remains an unmet need for individualized therapeutic approach in patients with DR.

Prevention of difficult-to-treat entities such as macular edema, iris and retinal neovascularization, and high-risk proliferative DR may become possible by early characterization of genomic features in every individual.

Personalized medicine in DR must also focus on individualization of glycemic target control, HbA$_{1c}$ levels, blood pressure, and lipid-lowering strategies. There has been only modest progress in the pharmacogenomics of glucose-lowering medications.[90] Largely, the treatment of diabetes thus far remains empirical.[95]

Because of the wide variation in the clinical presentation, progression, and complications of DR, certainly a tailored therapeutic approach may be more effective. Personalized medicine can be also helpful in DR prediction and prevention. With advances in the identification of potential genetic associations of high-risk genes such as the *1704T* allele (*RAGE* gene)[96] and *MTHFR 677C/T* polymorphisms,[97–99] data from proteomics and genomics may soon become relevant in clinical practice.[100]

## Clinical developments in treatment strategies based on pharmacogenomics

The availability of information on various genetic influences on the incidence and severity of DR has enabled newer treatment options targeting molecular pathways to be on the horizon. Studies have been initiated in order to target alternate pathways, such as the insulin-like growth factor pathway and tyrosine kinase (TIE-2) pathway, which may be overactive in certain sets of patients based on their genetic composition.[101,102]

RNA interference (RNAi) technology has been used to potentially identify newer therapeutic targets for DR.[103] RNAi allows silencing of practically any gene that may be overactive and responsible for phenotype manifestations resulting in disease. Such properties provide a promising strategy to treat diseases such as DR or DME.

Gene therapy for DR is still in its infancy. Animal studies have been initiated to deliver targeted molecules using adeno-associated virus to improve manifestations of DR with success.[104,105] There have been no definitive data to support full clinical usage.

## Future of pharmacogenomics and personalized medicine in diabetic retinopathy

The era of pharmacogenomics will undoubtedly allow tailoring treatment based on the individual's genetic profile.

Such a critical step will help to select the best therapy for the patient that will aid achieving the best visual outcome at the least possible cost. Future research strategies focusing on the identification of more phenotypic variations in DR based on clinical characteristics of the disease are certainly very relevant. In addition, consolidation of knowledge on genomic biomarkers of DR associated with suboptimal treatment response is necessary. It is imperative for clinical trials focusing on DR to analyze the possible reasons behind incomplete response or no response.

There have been advances in pharmacogenomics in other ocular diseases such as AMD and glaucoma. Therefore, further knowledge on the polymorphisms of the VEGF gene in DR and development of newer molecules to target the "resistant" allele may help improve visual outcomes in a larger number of patients. The level of evidence from various studies and practice guidelines will continue to evolve as more research is conducted in the field of pharmacogenomics.

## Disclosure

Quan Dong Nguyen and Diana V. Do serve on the Scientific Advisory Boards for Genentech, Inc. and Regeneron, Inc. The authors report no other conflicts of interest in this work.

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